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Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964–2003

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Population-based cancer registries are widely used to provide key information about cancer incidence, survival, determinants of progression and clues about pathogenesis. To substantially expand the limited data on diagnostic accuracy and completeness for lymphoproliferative (LP) tumors in such databases, we conducted a retrospective investigation of close to 1,000 cases diagnosed during 4 decades in Sweden. We identified and reviewed medical records for 494 LP tumor patients reported to the population-based Swedish Cancer registry and 503 LP tumor patients identified from hospitals in Sweden among patients with LP tumors diagnosed during 1964–2003. The stratified samples were randomly selected from patients according to LP subtype, over 4 equal calendar periods, and among 6 selected hospitals of diverse size and from different geographic regions. We found 97.9% of reported LP tumor cases to fulfill current diagnostic criteria for having an LP tumor and observed 89.7% to have accurate LP tumor subtype. The overall completeness of non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma cases in the Cancer registry was 95–99% but was lower for the more indolent tumors, chronic lymphocytic leukemia (87.9%) and Waldenström's macroglobulinemia (68.1%). We observed increased overall under-ascertainment for patients diagnosed above age 80 (27%) and among individuals diagnosed before 1973 (12%). In conclusion the diagnostic accuracy and completeness for classically defined LP tumor entities in the Swedish Cancer registry is high. However, we found under-ascertainment of patients with indolent LP tumors, particularly among patients diagnosed at older ages, with early-stage disease and diagnosed in earlier years.

Key words: diagnostic accuracy; ascertainment; non-Hodgkin lymphoma; Hodgkin lymphoma; multiple myeloma; chronic lymphocytic leukemia; Waldenström's macroglobulinemia; lymphoproliferative malignancies

Population-based cancer registries provide key information about cancer incidence for specific cancers according to subtype, and histopathology, patterns of survival and other aspects related to cancer treatment. Information about the patterns of specific cancers by age and gender is crucial for the design of clinical trials, for health care planning needs and for potential clues about etiology and determinants of progression. Some studies examining population-based cancer registries have indicated systematic problems in the completeness of reporting within certain population subgroups, such as older patients, or for patients whose malignancies are characterized by more indolent features.[1–4] For hematopoietic lymphoproliferative (LP) malignancies, there are only limited, if any, data available on potential variation in the accuracy and completeness of LP cancer diagnoses overall and within specific subgroups.

Since the mid-1950s Sweden has provided universal medical health care available for the entire population, currently ~9 million people. All physicians and pathologists are obliged by law to report incident cancer cases to the central population-based Swedish Cancer registry which was established in 1958.[1] Because of its large size and unique features including digital record-linkage with other unique central databases with nationwide coverage (*e.g.*, Multigenerational, Inpatient, Twin and Causes of Death registries), the Swedish Cancer registry has been widely used to study associations between personal or family history of certain defined diseases and subsequent risk of cancer, with the aim to provide etiologic and pathogenetic clues.[5–19] Also, by linking the Swedish Cancer registry to hospital-based routine diagnostic and treatment databases across the country, important large population-based studies have been conducted to examine risks of second malignancies among cancer survivors, and quantify second cancer risks in relation to radiation therapy, specific chemotherapy agents, combined modality treatments and combinations of other known carcinogens with radiation therapy.[20–22] Clearly, a large number of research studies based on the Swedish Cancer registry have had high impact on clinical practice and our thinking about certain diseases.

Among other goals, the population-based cancer registry offers a unique and special opportunity to conduct a detailed investigation of the accuracy and completeness of tumor diagnoses. To substantially expand the limited knowledge on this topic, we have conducted a large population-based investigation including detailed clinical information for close to 1,000 LP tumor patients diagnosed in Sweden 1964–2003. Aims of this investigation were to estimate the degree of completeness and diagnostic accuracy for LP tumors reported to the Swedish central cancer registry. The study of LP neoplasms is of particular interest since growing knowledge of immunology and immunogenetics in recent years has contributed to better definitions of distinct LP tumor entities and to the development of more precise tools to achieve greater diagnostic accuracy.[23]

Patient and methods

As described in detail below, 2 study populations of LP tumor patients were evaluated in this investigation; one was recruited from the Swedish Inpatient registry (hospital-based population) and one from the Swedish Cancer registry (registry-based population) each targeting about 500 patients. Each of the 2 study populations was selected from 6 hospitals of diverse size and located in different geographic regions (South, West, East and Middle Sweden). The hospitals included 4 regional University hospitals (Lund University hospital, Malmö University hospital, Sahlgrenska University hospital, and Karolinska University hospital) and 2 nonUniversity hospitals (Halmstad hospital and Borås hospital). We defined 4 calendar periods: 1964–1973, 1974–1983, 1984–1993 and 1994–2003. Five major categories of LP malignant entities were included in this study: non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM), chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia

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(WM) (Appendix). In the beginning of the study period, the LP cases were classified using the Kiel diagnostic classification which was utilized by most hematopathologists in Sweden.[24] In the mid-1990s, it was replaced by the more developed REAL classification,[25] which evolved into the current WHO classification. The WHO classification was described in 2001[23] and applied subsequently. The hospital-based and the registry-based study populations were defined as described below.

Source and selection of the hospital-based study population

The Swedish Inpatient registry has been in operation since 1964 and contains nationwide information on discharge diagnoses and discharge listings from inpatient care.[26] During the January 1, 1964 to December 31, 2003 study period, all hematology/oncology clinics were centralized to 10 regional University hospitals, which offer inpatient hospital care to a defined primary catchment area population (typically 100,000–150,000 inhabitants) in addition to being the referral center for a whole health care region. The remaining hospitals in the country serve regions with 30,000–100,000 inhabitants and offer inpatient hospital care.

We charged the National Board of Health and Welfare to apply a computerized algorithm to select a stratified random sample of cases from Swedish Inpatient registry. A total of 8 patients diagnosed with NHL and 4 patients each with HL, CLL, MM and WM who were newly diagnosed with these malignancies in each of the 4 periods at each study hospital Table II). Using this strategy, a total of 595 patients were selected from all study hospitals.

Source and selection of the registry-based study population

Information on every incident patient diagnosed with a malignant disorder in Sweden has to be reported to the centralized, nationwide Swedish Cancer registry which has been in operation since January 1, 1958.[1,7] In the present study we limited the selection of LP case subjects to those diagnosed after January 1, 1964, because information on hospitalization discharge visits is not available in the Swedish Inpatient registry prior to that date.[26] Thus, we wanted the hospital-based and the registry-based study populations (see later) to cover the same study period. Every physician and pathologist/cytologist is obliged by law to report each case of cancer to the registry. For each LP case, the Swedish Cancer registry contains information on histopathological diagnosis, sex, date of birth, date at diagnosis, and hospital where the diagnosis was made. Each individual in Sweden receives a unique personal identification number and every death along with the date of death is recorded and centralized in the causes of death register.

Similar to the approach we used for selecting the hospital-based study population, we requested the National Board of Health and Welfare to apply a computerized algorithm to select a stratified random sample of LP cases from Swedish Cancer registry. A total of 8 patients diagnosed with NHL and 4 patients with HL, CLL and MM, respectively, were identified during each of the 4 calendar-year periods at each hospital (Table II). Because WM is a very rare disease and since the majority of WM cases have been coded as "NHL unspecified" in the Swedish Cancer registry for most of the study years, we decided not to include WM cases in the registry-based study population.

Clinical data collection and outcome measures examined in both study populations

We retrieved available patient records and underlying relevant documentation for all patients in both study populations. For each patient, we reviewed medical records, laboratory results and underlying relevant clinical documentation. All pathology reports at primary diagnosis were reviewed by one of us (IT). The date of diagnosis was captured from pathology reports, and if the date was missing (<10%) we used the diagnosis date given in the medical record. We assessed the given LP tumor diagnosis in relation to current up-to-date diagnostic criteria (Appendix); after review we categorized all patients into 4 groups (Groups A-D; Table I) as shown in Table I and described in Appendix. We considered a patient to have an LP tumor if the person was categorized to belong to Groups A-C. For CLL patients, absence or presence of splenomegaly was registered as a surrogate marker for early *versus* more advanced disease.

TABLE I – CATEGORIES AND GROUPS OF DIAGNOSTIC ACCURACY

Category/Group	Comment[1]
Patient considered to have a lymphoproliferative tumor	
Group A	Diagnosis and classification of lymphoproliferative tumor is correct
Group B	Diagnosis of lymphoproliferative tumor correct, but classification is incorrect/not supported by data
Group C	Diagnosis of lymphoproliferative tumor probable but not unequivocally confirmed by data
Patient considered not to have a lymphoproliferative tumor	
Group D	Without evidence of a lymphoproliferative tumor

[1]Applied diagnostic criteria for non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia are given in Appendix.

Approval was obtained from the Swedish National Ethics review board for these studies (approval No. 2005/206-31/3). Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the NIH Office of Human Subjects Research because NIH/NCI had no access to data with personal identifiers.

Statistical analysis

For each LP case, the diagnosis from pathology reports in medical records or from the cancer registry was reviewed and a level of diagnostic accuracy was assigned. We calculated the percent of the total LP cases in each category according to the level of diagnostic accuracy by dividing the number of cases in each category by the total number designated as LP cases. This was performed separately for the hospital ascertained and the registry ascertained cases. Further, we estimated the completeness of LP tumor cases reported to and listed in the Swedish Cancer registry. We ascertained the fraction of LP tumor cases in the hospital-based study population that were appropriately recorded to the Swedish Cancer registry. Finally, we estimated the proportion of LP tumor cases with a delayed reporting (3 months or more after diagnosis) to the registry. χ^2 and Fisher exact tests were used for contingency tables.

Results

Altogether, 591 and 595 patients with reported LP tumors were included in the registry-based and the hospital-based study populations, respectively. Patient records could be found and obtained for 494 (83.6%) and 503 (84.5%) of the patients. Close to two thirds (64.9%) of missing records were from the first calendar period (1964–1973).

Diagnostic accuracy of lymphoproliferative tumors

Registry-based study population. The overall proportion of cases that were correctly registered as having an LP tumor diagnosis (Groups A, B and C) was 98.0% (484/494) (Table II). The fraction of cases that were correctly diagnosed and classified (Group A) was close to 90% (438/494): CLL (77.2%), MM (93.1%), NHL (87.9%) and HL (97.1%). Among remaining 56 cases, an LP malignancy was documented but the type of LP tumor was misclassified (Group B) in 39 cases; either the LP tumor type was incorrect ($n = 26$) or the underlying information was inconclusive ($n = 13$). In 7 cases, the LP tumor diagnosis was likely but not

TABLE II – DIAGNOSTIC ACCURACY OF HEMATOPOIETIC LYMPHOPROLIFERATIVE TUMORS[1], *N* (%)

Category	Registry-based study population		Hospital-based study population		Combined	
Total number of patients	494	(100)	503	(100)	997	(100)
NHL	189	(100)	106	(100)	295	(100)
HL	103	(100)	100	(100)	203	(100)
CLL	101	(100)	101	(100)	202	(100)
MM	101	(100)	103	(100)	204	(100)
WM	NA	NA	93	(100)	93	(100)
The patient has an LP tumor diagnosis, total	484	(98.0)	492	(97.8)	976	(97.9)
Diagnosis and classification correct, total (Group A)	438	(88.7)	456	(90.7)	894	(89.7)
NHL	166	(87.9)	97	(91.5)	263	(89.2)
HL	100	(97.1)	86	(86.0)	186	(91.6)
CLL	78	(77.2)	91	(90.1)	169	(83.7)
MM	94	(93.1)	96	(93.2)	190	(93.1)
WM	NA	NA	86	(92.5)	86	(92.5)
Diagnosis established but classification incorrect/not supported by data, total (Group B)	39	(7.9)	31	(6.2)	70	(7.0)
NHL	14	(7.4)	2	(1.9)	16	(5.4)
HL	3	(2.9)	11	(11.0)	14	(6.9)
CLL	16	(15.8)	7	(6.9)	23	(11.4)
MM	6	(5.9)	6	(5.8)	12	(5.9)
WM	NA	NA	5	(5.4)	5	(5.4)
Diagnosis probable but not unequivocally confirmed by data, total (Group C)	7	(1.4)	5	(1.0)	12	(1.2)
NHL	4	(2.1)	3	(2.8)	7	(2.4)
HL	0	(0)	1	(1.0)	1	(0.5)
CLL	3	(3.0)	1	(1.0)	4	(2.0)
MM	0	(0)	0	(0)	0	(0)
WM	NA	NA	0	(0)	0	(0)
Without evidence of an LP tumor, total (Group D)	10	(2.0)	11	(2.2)	21	(2.1)
NHL	5	(2.6)	4	(3.8)	9	(3.1)
HL	0	(0)	2	(2.0)	2	(1.0)
CLL	4	(4.0)	2	(2.0)	6	(3.0)
MM	1	(1.0)	1	(1.0)	2	(1.0)
WM	NA	NA	2	(2.2)	2	(2.2)

[1]The following ICD-codes were applied: non-Hodgkin lymphoma (NHL) (ICD-7:200, 202; ICD-9: 200, 202; ICD-10: C82-C85), Hodgkin lymphoma (HL) (ICD-7: 201; ICD-9: 201; ICD-10: C81), chronic lymphocytic leukemia (CLL) (ICD-7: 204.1; ICD-9: 204.1; ICD-10: C91.1), Waldenström's macroglobulinemia (WM) (ICD-8: 275.5; ICD-9: 273D; ICD-10: C88), and multiple myeloma (MM) (ICD-7: 203; ICD-9: 203.0; ICD-10: C90.0).

unequivocal (Group C), and in 10 cases the review did not support a diagnosis of an LP malignancy (Group D).

The largest proportion of cases with a revised diagnosis to another type of LP tumor were patients initially given a CLL diagnosis (13%; 13/101). Patients were reclassified to the following diagnoses: diffuse well differentiated lymphocytic lymphoma ($n = 4$); immunocytoma ($n = 3$); hairy cell leukemia ($n = 2$); prolymphocytic leukemia ($n = 1$); splenic lymphoma with villous lymphocytes ($n = 1$); large granular lymphocytic leukemia ($n = 1$) and due to coding errors, there was one MM case. Among patients with LP tumors other than CLL; we found 5 MM cases that we reclassified as solitary plasmocytoma ($n = 3$) or monoclonal gammopathy of undetermined significance ($n = 2$). Five NHL cases were reclassified as HL ($n = 2$), CLL ($n = 2$), and acute lymphocytic leukemia ($n = 1$). Three HL cases were revised to NHL of the following subtypes: reticulum cell sarcoma ($n = 1$), immunoblastic lymphoma ($n = 1$) and diffuse large B-cell lymphoma ($n = 1$).

Among the 10 cases without support for a LP tumor diagnosis, 4 cases were due to coding errors by the Swedish Cancer registry since there was a correct non-LP tumor diagnosis in the medical record; however, 6 cases were incorrectly diagnosed and reported as LP tumors when the correct diagnosis was other type of malignancies (myelodysplastic syndrome or anaplastic gastric cancer) or benign conditions (folliculitis, actinic reticuloid, reactive plasmocytosis and benign lymphocytosis).

The proportion of LP tumor cases that were both correctly diagnosed and classified (Group A) increased over time, from 77.8% in the earliest period (1964–1973) to 93.6% in the most recent period (1994–2003). Conversely, the proportion of cases with an incorrect classification according to the review (Group B) decreased from 10.1 to 5.7% between the earliest and latest calendar periods, respectively (Table III).

Hospital-based study population. A total of 492/503 (97.8%) LP tumors were found to be correctly diagnosed (Groups A, B, and C) (Table II). The median age at diagnosis was lower in HL (38 years) but did not differ substantially between the other LP categories (NHL 66, MM 70, CLL 69 and WM 70 years). The proportion of cases that were correctly diagnosed and classified (Group A) was 90.7% (456/503). Among remaining 47 cases, the classification was either incorrect ($n = 24$) or there were insufficient data for classification ($n = 7$) (Group B); in 5 cases, an LP tumor diagnosis was likely but not unequivocal (Group C); and in 11 cases the diagnosis was either wrong or incorrectly reported (Criteria D) (Table II).

We revised the diagnosis to another type of LP tumor in the following number of cases: 5 CLL cases were reclassified to well differentiated lymphocytic lymphoma ($n = 3$), immunocytoma ($n = 1$), and centrocytic lymphoma ($n = 1$); 6 MM cases were revised to solitary plasmocytoma ($n = 3$), MGUS ($n = 2$) and HL ($n = 1$, coding error with correct diagnosis in hospital record); one NHL case was reclassified to CLL, and 8 HL cases had their diagnosis revised to NHL (centroblastic/centrocytic ($n = 2$), immunocytoma ($n = 1$), immunoblastic ($n = 1$), poorly differentiated lymphocytic, diffuse ($n = 1$), Burkitt ($n = 1$), lymphoepitheloid T-cell ($n = 1$) and centroblastic ($n = 1$)). The diagnoses of 4 WM cases were revised to IgM MGUS. Among 11 cases without support for an LP tumor diagnosis, 8 cases were incorrectly diagnosed as LP malignancies in the Cancer registry, although postdiagnosis corrections were documented in the patients' records for 6 of these 8 patients. However, the revised diagnosis in the medical records was apparently not reported to the Swedish Cancer registry. For

TABLE III – DIAGNOSTIC ACCURACY OF HEMATOPOIETIC LYMPHOPROLIFERATIVE TUMORS[1] ACCORDING TO PERIOD, *N* (%)

Category	Registry-based study population		Hospital-based study population		Combined	
Total number of patients	494	(100)	503	(100)	997	(100)
1964–1973	99	(100)	118	(100)	217	(100)
1974–1983	119	(100)	131	(100)	250	(100)
1984–1993	135	(100)	146	(100)	281	(100)
1994–2003	141	(100)	108	(100)	249	(100)
The patient has an LP tumor diagnosis, total	*484*	(98.0)	492	(97.8)	976	(97.9)
Diagnosis and classification correct, total (Group A)	438	(88.7)	456	(90.7)	894	(89.7)
1964–1973	77	(77.8)	107	(91.2)	184	(84.8)
1974–1983	107	(89.9)	117	(89.3)	224	(89.7)
1984–1993	122	(90.4)	133	(91.1)	255	(90.7)
1994–2003	132	(93.6)	99	(91.7)	231	(92.8)
Diagnosis established but classification incorrect/not supported by data, total (Group B)	39	(7.9)	31	(6.1)	70	(7.0)
1964–1973	10	(10.1)	9	(7.6)	19	(8.3)
1974–1983	11	(9.2)	11	(8.4)	22	(8.8)
1984–1993	10	(7.4)	6	(4.1)	16	(5.7)
1994–2003	8	(5.7)	5	(4.6)	13	(5.9)
Diagnosis probable but not unequivocally confirmed by data, total (Group C)	7	(1.4)	5	(1.0)	12	(1.3)
1964–1973	4	(4.0)	1	(0.8)	5	(2.3)
1974–1983	1	(0.8)	2	(1.5)	3	(1.2)
1984–1993	1	(0.7)	1	(0.7)	2	(0.7)
1994–2003	1	(0.7)	1	(0.9)	2	(0.8)
Without evidence of an LP tumor, total (Group D)	10	(2.0)	11	(2.2)	21	(2.1)
1964–1973	8	(8.1)	1	(0.8)	9	(4.1)
1974–1983	0	(0)	1	(0.8)	1	(0.4)
1984–1993	2	(1.5)	5	(3.4)	7	(2.5)
1994–2003	0	(0)	4	(3.7)	4	(1.6)

[1]The following ICD-codes were applied: non-Hodgkin lymphoma (NHL) (ICD-7:200, 202; ICD-9: 200, 202; ICD-10: C82-C85), Hodgkin lymphoma (HL) (ICD-7: 201; ICD-9: 201; ICD-10: C81), chronic lymphocytic leukemia (CLL) (ICD-7: 204.1; ICD-9: 204.1; ICD-10: C91.1), Waldenström's macroglobulinemia (WM) (ICD-8: 275.5; ICD-9: 273D; ICD-10: C88), and multiple myeloma (MM) (ICD-7: 203; ICD-9: 203.0; ICD-10: C90.0).

TABLE IV – COMPLETENESS OF SPECIFIED HEMATOPOIETIC LYMPHOPROLIFERATIVE TUMORS IN THE SWEDISH CANCER REGISTRY, STRATIFIED BY CALENDAR PERIOD, AGE-GROUP, GENDER, AND HOSPITAL CATEGORY

Variable	NHL		HL		MM		CLL		WM		Combined	
	Total	Obs (%)	Total	Obs (%)	Total	Obs (%)	Total	Obs (%)	Total	Obs (%)	Total	Obs (%)
Calendar period												
1964–1973	24	23 (95.8)	20	20 (100)	26	25 (96.2)	29	27 (93.1)	18	8 (44.4)	117	103 (88.0)
1974–1983	24	24 (100)	23	23 (100)	27	25 (92.6)	26	21 (80.8)	30	20 (66.7)	130	113 (86.9)
1984–1993	28	28 (100)	32	32 (100)	26	26 (100)	28	25 (89.3)	27	23 (85.2)	141	134 (95.0)
1994–2003	26	23 (88.5)	23	22 (95.7)	23	21 (91.3)	16	14 (87.5)	16	11 (68.8)	104	91 (87.5)
Combined	102	98 (96.1)	98	97 (99.0)	102	97 (95.1)	99	87 (87.9)	91	62 (68.1)	492	441 (89.6)
Age-group												
50 or lower	21	20 (95.2)	52	52 (100)	13	13 (100)	7	6 (85.7)	3	3 (100)	96	94 (97.9)
51–60	19	19 (100)	13	13 (100)	17	16 (94.1)	17	17 (100)	12	8 (66.7)	78	73 (93.6)
61–70	20	19 (95.0)	14	14 (100)	23	20 (87.0)	32	28 (87.5)	30	23 (76.7)	119	104 (87.4)
71–80	35	34 (97.1)	13	12 (92.3)	41	40 (97.6)	29	26 (89.7)	33	23 (69.7)	151	135 (89.4)
81 or higher	7	6 (85.7)	6	6 (100)	8	8 (100)	14	10 (71.4)	13	5 (38.5)	48	35 (72.9)
Gender												
Male	55	53 (96.4)	61	60 (98.4)	59	56 (94.9)	62	57 (91.9)	59	43 (72.9)	296	269 (90.9)
Female	47	45 (95.7)	37	37 (100.0)	43	41 (95.3)	37	30 (81.1)	32	19 (59.4)	196	172 (87.8)
Hospital category												
University	68	67 (98.5)	70	69 (98.6)	72	69 (95.8)	66	60 (90.9)	68	48 (70.6)	344	313 (91.0)
Nonuniversity	34	31 (91.2)	28	28 (100)	30	28 (93.3)	33	27 (81.8)	23	14 (60.9)	148	132 (89.2)

NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukemia; WM, Waldenström's macroglobulinemia; Total, cases in the hospital-based study population with a hematolymphoproliferative malignancy considered to be accurate (see Table II); Obs, number of cases (among the "total") with the same recorded hematolymphoproliferative malignancy in the Swedish Cancer registry as given in the patient record.

remaining 3 cases without support for an LP tumor diagnosis, the diagnosis in the patient record was a non-LP tumor diagnosis and the cause was thus purely a reporting error in the registry.

The proportion of LP tumor cases that were both correctly diagnosed and classified (Group A) increased over time, from 84.8% (1964–1973) to 92.8% (1994–2003). Conversely, the proportion of cases with an incorrect classification of the LP tumor according to the review (Group B) decreased from 8.3 to 5.9% between the first and last calendar periods (Table III).

Completeness of the Swedish Cancer registry

We used the hospital-based study population to assess the completeness of reporting to the Swedish Cancer registry. We found that 441/492 (89.6%) of the patients diagnosed with an LP tumor in any of the 6 included hospitals were subsequently reported to the registry (Table IV). The distribution of cases not reported to the Cancer Registry among the total LP cases in each major category was as follows: NHL 4/102, HL 1/98, MM 5/102, CLL 12/99 and WM 29/91. Among patients in the hospital-based-population

with a CLL diagnosis, underreporting to the registry was more common among patients without (8/23; 34.8%) *versus* with (4/72; 5.6%) splenomegaly, respectively (Fisher exact test, $p = 0.001$). We found no evidence of variation by calendar period for any of the LP tumors, with the exception of WM where the proportion of reported cases increased during the first 3 periods (1964–1973: 44.4%; 1974–1983: 66.7%; 1984–1993: 85.2%) and then it decreased again (1994–2003: 68.8%; Table IV).

The median age at diagnosis among patients reported to the Swedish Cancer registry was 66 years and the proportion of patients diagnosed above the age of 80 years was 8.0% (35/441). Patients who were not reported to the registry had a median age of 74 years and 25.5% (13/51) were 80 years or older. The overrepresentation of older patients among those who were not reported to the registry did not vary over time (data not shown).

When we assessed the fraction of missing LP tumor cases in the Swedish Cancer registry by hospital category, we found that 9.0 and 10.2% of the patients diagnosed in University and non-University hospitals, respectively, were not recorded in the registry. There was no overall gender difference in reporting; however, the under-ascertainment of CLL and WM was more pronounced among women (Table IV). For 93.2% of the patients, the date of diagnosis recorded in the Swedish Cancer registry was delayed less than 3 months compared to the date of diagnosis in the patient record. Thus, the date of reporting the LP case in the Cancer registry was 3 or more months delayed (range 3–75 months) for 6.8% of the cases. The distribution of LP tumors with a 3 or more months delayed date of diagnosis was as follows: NHL (2/102), HL (2/98), MM (9/102), CLL (6/99) and WM (11/91).

Discussion

In this large population-based study including 997 patients diagnosed with a LP malignancy during 4 decades (between 1964 and 2003) in Sweden, we found almost 98% diagnostic accuracy. While the overall completeness of NHL, HL and MM cases reported to the Swedish Cancer registry was more than 95%, we observed underreporting of individuals with more indolent types of LP malignancies. The completeness of CLL and WM were 87.9 and 68.1% respectively. Underreporting was higher for individuals with early-stage disease, patients who were diagnosed at older ages, and persons diagnosed in earlier calendar periods. These findings have important clinical and scientific implications for the design and interpretation of results from population-based studies on LP tumors.

This study adds substantially to the limited data on this topic. To our knowledge, this is the largest investigation examining the diagnostic accuracy and completeness of reporting of most types of LP malignancies to population-based cancer registries. In a few previous studies with main focus on solid tumors, investigators have assessed population-based cancer registries in the U.S. and in Europe and found evidence of under-ascertainment and heterogeneity of diagnostic accuracy. A prior study based on the Swedish Cancer registry used death certificates from the year 1978 as the reference for comparison and found a deficit of 4.5% for all types of cancer,[1] but 16% of deaths from MM and 18% of deaths from leukemia had not been reported. Another Swedish study based on 260 acute leukemia cases diagnosed 1987–1992 observed 15.4% under-ascertainment in the Swedish Cancer registry.[2] Further, a previous Swedish study found 6.7% under-ascertainment of malignant lymphomas in a subset of the Swedish Cancer registry covering Uppsala County 1969–1987,[27] and 5.9% of the cases were found not to have lymphoma following a review of 639 histopathological specimens. A deficit of 8.9% was observed in a study based on 13,531 cases using the statewide Florida Cancer registry.[3] A review of 7,043 patients whose discharge diagnoses of cancer were recorded in the Northern Ireland Cancer registry revealed that 7.4% of these cases did not have a malignancy.[28] While the Thames Cancer registry in the U.K. attained 92.1% completeness of reporting 5 years after diagnosis for all cancers,[29] a sub-study indicated that 30% of 4,714 patients with a hematopoietic malignancy were not reported to the registry, and 20% of the hematopoietic tumors were inappropriately classified.[30] A study based on the Finnish Cancer registry (1985–1988) based on 68,628 cases found a deficit of 1.4% for cancer in general, but for hematopoietic cancers ($n = 4,906$) the rate was substantially higher (7.9%).[4] In a population-based study from Tromsö in Norway the underreporting of hematopoietic malignancies was found to be as high as 14% based on 114 cases.[31]

Although the overall diagnostic accuracy and completeness of reporting was high, there was some heterogeneity by type of LP tumor. For MM, both the diagnostic accuracy of individual cases and the completeness of the Swedish Cancer registry were very high in contrast to the study aforementioned.[1] Only 4/204 patients with a MM diagnosis were actually found to have a diagnosis of MGUS, indicating a high degree of distinction between premalignant and malignant disease.

For NHL and HL cases, we similarly found the under-ascertainment to be low (3.9 and 1.0%, respectively), in contrast with 6.7% under-reporting of lymphoma cases from the prior Swedish study restricted to Uppsala County (34). Among HL cases, the original diagnosis was changed to NHL of various types in 5.4% (11/203) of the cases; 8 of 11 of these were diagnosed during the first 2 decades of the study period. This probably reflects diagnostic improvements over time to better distinguish pleomorphic and giant tumor cells from Hodgkin cells and Reed-Sternberg cells.[23] Unfortunately, because of multiple changes in the classification systems of NHL during the 40-year study period, it was not possible to analyze NHL cases originally designated as HL according to NHL subtype.

In CLL, both the completeness (87.9%) and diagnostic accuracy (83.7%) was lower compared to MM, NHL and HL. The most common revised diagnosis was well-differentiated lymphocytic lymphoma which accounted for 4.0% of the cases. Although CLL is distinguished from this entity by the presence of a clear leukemic manifestation, possible reasons for the misclassification may include diagnostic assessment restricted to biopsy or combined grouping of these 2 entities. Because early-stage CLL does not require treatment, clinicians may be less prone to report these to the Cancer registry. Unfortunately, complete information required for staging according to the Rai or Binet staging systems for CLL[32,33] is not systematically reported to the Swedish Cancer Registry. We therefore used absence or presence of splenomegaly as a surrogate marker of early *versus* advanced disease and found underreporting to be significantly more common among early-disease (34.8%) than advanced (5.6%) CLL cases. Our data suggest that there is no evidence of increased reporting of early-stage CLL cases in the registry in more recent years.

The most pronounced under-ascertainment occurred among WM cases, which was highest in the earliest calendar period and among older patients. The delay in reporting WM cases to the registry of more than 3 months was 12%, which is substantially higher than other LP tumors under study. Possible reasons may include the indolent nature of some WM cases or initial misdiagnosis. Importantly, only 4 WM cases were reclassified as IgM MGUS cases indicating a high diagnostic accuracy for WM cases. It is likely that the improved ascertainment of WM cases over time is due to more comprehensive and better diagnostic work-up and/or newer classification of WM as a malignant neoplasm, whereas previously WM had been categorized as a benign disorder.[23–25]

As aforementioned, Sweden provides universal medical health care for the entire population. In sharp contrast to, for example, the U.S. (where the majority of LP tumor patients are primarily seen and treated by doctors outside hospitals in private practice), LP tumor patients in Sweden are almost exclusively being diagnosed, treated and followed clinically by physicians at hospital-based hematology/oncology units which provide both inpatient

and outpatient care. Clinicians working in such units typically see patient both in the inpatient and the outpatient clinics.

Strengths of this study include the long study period and the detailed review of available medical records and underlying documentation for a stratified random sample of close to 1,000 LP tumor cases in order to assess the accuracy of the diagnosis. By comparing and contrasting across all LP malignancies, we can improve understanding of misclassification within this major group of related malignancies. Other strengths include the population-based design with 6 selected hospitals of varying size and geographic region, thus allowing generalizability.

Limitations include problems in identifying or locating early hospital-based patients' records and underlying documentation. Histopathology assessment of diagnoses was based on the pathology report, since it was beyond the scope of the investigation to cut new sections of tumor tissue or to restain new or existing slides with reagents to help improve histopathology assessment. This incomplete characterization of LP cases prevented us from conducting more detailed sub-analyses. Another potential limitation is the use of the nationwide Inpatient registry to identify persons with LP tumors for the hospital-based study population. Thus any cases diagnosed only as outpatients would not be sampled and could not be evaluated for completeness of cancer registration. The reason why we used the Inpatient registry was simply because of the fact that the hospitals did not have any reliable internal tracking systems allowing us to identify randomly selected LP tumors for the defined calendar periods. Studies based on outpatient hospital registries are needed to evaluate the completeness of registration of indolent LP diseases.

Our findings of 95% completeness for NHL, HL and MM, but some evidence of under-reporting of CLL and WM suggest that use of the registry alone for the latter may reflect incomplete risk factors (such as survival experience or biological characteristics of more indolent forms of CLL and WM) or occurrence of these entities in older patients, particularly women. Our data also suggest that a concerted effort needs to be made to encourage more complete reporting of CLL and WM patients seen outside of the hospital setting. Nevertheless, overall the high quality of diagnostic accuracy and more than 95% complete reporting of LP cases to the Swedish Cancer registry support the continued use of this valuable resource for etiologic, clinical, survival and mechanistic studies of LP malignancies.

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Appendix – Diagnostic criteria for non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia

Non-Hodgkin lymphoma

Surgical biopsy of tumor (lymph node or extranodal tissue) with adequate pathological report compatible with diagnosis of NHL or Documentation of lymphadenopathy, splenomegaly or extranodal tumor and aspiration biopsy of tumor (lymph node or extranodal tissue) with adequate description of abnormal lymphocyte population compatible with NHL. If immunophenotyping is performed it should confirm the diagnosis.

Hodgkin lymphoma

Surgical biopsy of tumor (lymph node or extranodal tissue) with adequate pathological report compatible with diagnosis of HL or Documentation of lymphadenopathy, splenomegaly or extranodal tumor and aspiration biopsy of tumor (lymph node or extranodal tissue) with adequate description of abnormal lymphocyte population compatible with HL. If immunophenotyping is performed it should confirm the diagnosis.

Multiple myeloma

Serum M-protein $\geq$3.0 g/dL and increased number of bone marrow plasma cells and/or Bone marrow clonal plasma cells $\geq$10% or M-protein in serum or urine irrespective of concentration in combination with myeloma increase of plasma cells in bone marrow and related organ or tissue impairment (osteolytic lesions, hypercalcemia, renal failure or anemia not caused by other disease).

Chronic lymphocytic leukemia

Peripheral blood lymphocytosis ($\geq 1.5 \times 10^9$/dL) not explained by other diseases in combination with domination of small, mature lymphocytes typical for CLL in blood smears and/or bone marrow biopsy or lymph node biopsy. If immunophenotyping is performed it should be CD19+/CD5+/CD 23+/Igdim.

Waldenström's macroglobulinemia

Serum M-protein of IgM type and Bone marrow *and/or* lymph node biopsy with infiltration of lymphoplasmacytic lymphoma (Refs. 25, 34–36).

*Classification into categories A–D was made by reviewing available clinical data as well as the pathology report**

- Category A. All criteria as described above are fulfilled
- Category B. An LP malignancy is unequivocally confirmed but a detailed analysis of the pathology report and/or other clinical data either supports reclassification to another of the 5 main categories of LP cancers or information is considered insufficient for correct classification.
- Category C. Clinical data and pathology report are compatible with but do not unequivoacally confirm a diagnosis of LP tumor.
- Category D. No evidence of an LP tumor is found in review of clinical data and pathology report.

*Examination of biopsy material was not performed. Four cases of Monoclonal Gammopathy of Undetermined Significance (MGUS) were included in group B although it is only a premalignant condition with potential to develop into LP.